REMARKS

Applicants have cancelled Claim 37, without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of the claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 22-27 and 35, incorporating functional limitation of the polypeptide encoded by the nucleic acid molecules of the invention. In the amendments set forth above additions are underlined and ~~deletions are struck through~~. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed.

Applicants respond below to the specific rejections and objections raised by the Examiner in the Office Action of April 28, 2003.

I. Priority

The Examiner has denied priority to PCT/US99/28551 and other provisional applications. Applicants respectfully submit that in a preliminary amendment filed on August 30, 2002, Applicants claimed priority to U.S. Serial No. 09/866,034, of which the present application is a continuation, and to PCT/US99/28634 and Serial No. 60/119,965. A copy of the preliminary amendment is attached herewith for the Examiner's convenient review.

The nucleic acid of SEQ ID NO:6, which is a subject matter of the presently pending claims, was first disclosed as Figure 1 in Serial No. 60/119,965, filed February 12, 1999. In addition, the same nucleic acid was disclosed as Figure 3 and SEQ ID NO:6 in PCT/US99/28634, filed December 1, 1999, and in Serial No. 09/866,034, filed May 25, 2001. Therefore, Applicants claim priority for SEQ ID NO:6 of the present application to at least December 1, 1999. An Application Data Sheet having the correct priority information is also being submitted herewith.

II. Objections and Rejections under 35 U.S.C. § 101

Claims 22-41 stand rejected under 35 U.S.C. § 101 for allegedly lacking specific and substantial asserted utility or a well established utility. The Examiner concedes on page 3, line 4, of the Office Action that the asserted utility in the present application is credible. For the reasons set forth below, Applicants respectfully traverse the Examiner's § 101 rejections.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

Applicants submit that the gene amplification data provided in the present application are sufficient to establish a specific and substantial utility for the PRO539 polypeptide.

Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 16 of the present application, the inventors isolated genomic

DNA from a variety of primary cancers and cancer cell lines that are listed in Table 7 (page 117 of the specification). As a negative control, DNA was isolated from the blood of normal healthy individuals (page 115, lines 22-33). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 7. As explained on page 112, lines 17-19, the results of TaqMan™ PCR are reported in ΔCt units. It is well-known in the art that "Ct" stands for "threshold cycle." One Ct unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification.

It is well-known in the art how ΔCt values are calculated. The TaqMan™ real-time PCR method, which is the used in the methods of the present application, has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The TaqMan™ 7700 Sequence Detector Software calculates the Ct values for each given experiment. Those of skill in the art know that to obtain ΔCt, the difference between the Ct values of the test sample and the normal sample is calculated. Furthermore, the specification itself teaches that "The diluted samples were used provided that the Ct value of the normal human DNA subtracted from test DNA was +/- 1 Ct." Specification at page 116, lines 30-31. Thus, the specification teaches that ΔCt is obtained when the Ct value of the normal sample is subtracted from the Ct value of the test sample.

As for the significance of the data, the specification states that one ΔCt unit corresponds to two-fold amplification, two units to four-fold, three units to 8-fold, etc. This fact is also well-known in the art. Thus, the significance of knowing the ΔCt value is that the extent of gene amplification in a cancer cell is known.

As set forth on page 85, lines 34-37, the disclosed proteins of the invention can be used for tissue typing. Table 7 identifies several tissue types, all obtained from cancerous tumors, in which PRO539 is amplified. PRO539 can then be used diagnostically in determining whether a particular tissue type obtained from a patient is cancerous or not. Thus, those of skill in the art recognize the utility of the PRO539 polypeptide as a diagnostic and therapeutic tool. This utility is specific, since it applies only to those polypeptides where the overexpression of their genes is established, i.e., PRO539 . The utility is also credible, because those of skill in the art recognize that having a diagnostic tool to identify cancer tissues before they have advanced to the point where the disease compromises the life-span of the individual patient, or a therapeutic tool to

treat the disease once the patient has been diagnosed with cancer, is quite attractive. Furthermore, the utility is substantial since it can potentially alert medical professionals to the presence of cancer at an early stage when treatment is facile and feasible.

In support of Applicants' assertion of utility, Applicants have submitted herewith a copy of the declaration of Dr. Audrey Goddard with exhibits A-G (the Goddard Declaration), originally submitted in a related and co-owned patent application Serial No. 09/903,925. As Dr. Goddard's *curriculum vitae*, Exhibit A of the Goddard Declaration, shows, she is an expert in the art of identifying and quantifying the amplification of oncogenes in cancers.

In her declaration, Dr. Goddard states that

> the quantitative TaqMan PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. It is further my considered scientific opinion that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

The Goddard Declaration, paragraph 7. Therefore, according to Dr. Goddard, a 2-fold increase, i.e., a ΔCt value of 1, not only is not of questionable significance, but is "significant and useful" in, *inter alia*, detecting cancerous tumors or the diagnosis of cancer. Thus, the Goddard Declaration support Applicants' position that the ΔCt value of 1 is significant and is outside of the experimental error of this procedure.

Applicants respectfully maintain that the present application as filed contained assertions of utility that go above and beyond the utility requirements set forth by the Office. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

III. Rejections under 35 U.S.C. § 112, First Paragraph: Written Description

Claims 22-26 and 35-41 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing a subject matter which is not described in the specification in such a way as to convey to one of skill in the art that the inventor had possession of the application. In setting

forth the rejection, the Examiner states that "no common element or attributes of the sequences are disclosed . . . . [¶] There is no showing or evidence which links structural limitations or requirements to any particular functional limitations." The Office Action, page 6, lines 16-19.

Applicants respectfully disagree. Those of skill in the art, having read the present specification, understand that the nucleic acid molecules of the present invention all share the unique function that they can be used as diagnostic tools for identifying pre-cancerous or cancerous cells, or as therapeutic tools for monitoring cancer developments or the efficacy of cancer treatment. Thus, all the nucleic acid molecules of the present invention share the same particular function. In order to further clarify the functional limitation shared by the molecules of the invention, and in order to advance the case towards allowance, Applicants have amended Claims 22-27 and 35 and have incorporated the functional limitation in the claims.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

IV. Rejections under 35 U.S.C. § 112, First Paragraph: Scope of Enablement

Claims 22-41 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing a subject matter which is not described in the specification in such a way as to enable one of skill in the art to make or use the invention. In setting forth the rejection, the Examiner at times refers to the nucleic acid molecules of the invention as those that encode PRO539 and at other times those that encode PRO1868. Applicants believe this to be a typographic error in the Office Action. The nucleic acid molecules of the present invention are those that encode PRO539.

Applicants have amended the claims to incorporate a functional limitation shared by the nucleic acid molecules of the present invention. The amendments made herewith reaffirm the fact that the full scope of the claims of the present invention is enabled.

The Examiner correctly cites *In re Wands* and the factors set forth therein to determine the scope of enablement. However, the Examiner's conclusions are not in line with the teachings of *Wands*. For example, given the recent advances in the science of molecular biology, the unpredictability of this art has lessened significantly. As a result, the number of experiments necessary to determine a particular result is now low, and these experiments have become routine in the art. The Examiner concedes that the level of skill in this art is very high, and thus ordinary

artisans are expected to be adept in various methodologies in this art and practice them routinely. The breadth of the claims are commensurate with the examples provided in the specification, where the use of nucleic acids encoding polypeptides that are used diagnostically or therapeutically for certain types of cancer is set forth in detail. Therefore, given the disclosure of the present invention, the level of skill in the present art, and the functional limitation of the present claims, Applicants respectfully submit that the present claims are fully enabled.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

V. Rejections under 35 U.S.C. § 102(b)

Claims 35-37 stand rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Hillier et al (GenBank Accession No. AI366107, January 7, 1999). In view of the cancellation of Claim 37, the rejection with respect to that claim is now moot.

Applicants respectfully traverse the rejection of Claims 35 and 36. Claim 35, as amended herewith, is drawn to a nucleic acid molecule that has at least 80% sequence identity to the complement of the nucleic acid molecule of SEQ ID NO:6. The Hillier sequence consists of 501 bases. Given that SEQ ID NO:6 consist of 3121 bases, even if the entirety of the Hillier sequence was identical to a portion of the complement of SEQ ID NO:6, such identity would amount to only a 16% sequence identity. Therefore, the Hillier sequence does not fall within the scope of the present claims. In other words, the Hillier sequence is too short to anticipate the nucleic acid molecules of Claims 35-36.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

VI. Specification

In reviewing the specification, Applicants encountered some inadvertent errors in numbering the tables and correlating figure numbers to sequence identification numbers. Applicants have herewith submitted amendments to the specification to correct these errors. Applicants submit that these amendments add no new matter and are fully supported by the specification as originally filed.

CONCLUSION

Applicants respectfully maintain that claims are patentable and request that they be passed to issue. No fee is believed due in connection with this response. If this is incorrect, the Commissioner is hereby authorized to charge Deposit Account No. 07-0630. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 8, 2003

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